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RESPONSE OF THE CARDIOVASCULAR SYSTEM TO VIBRATION AND COMBINED STRESSES.

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INTRODUCTION

The goal of this program over the last several years has been the understanding of cardiovascular responses to force-field loading of the total physiological system. These force fields may be due to earth gravity or forces produced by whole body acceleration. The acceleration forces may be either static, slowly-varying, or extremely fast, relative to the cardiovascular system's capability to respond. Understanding of these responses implies qualitative and quantitative evaluation of the cardiovascular changes produced by the acceleration loading and knowledge of the control mechanisms responsible for eliciting these adjustments.

Proper cardiovascular control is essential to the preservation of physiological integrity under varied environmental conditions. The circulation is maintained in a state of dynamic equilibrium by a number of pressure, volume and possible force-field sensitive, cardiac and vascular control mechanisms. Investigations of cardiovascular control using the systems analysis approach indicate that the dynamic frequency response of these control mechanisms is primarily limited to the range below 0.3 Hz (1-6). Consequently, effective circulatory control could be significantly challenged by environmental physiological stresses which are capable of generating systemic pressure or flow disturbances in this range. Low frequency, whole body g_z (spinal axis) acceleration loadings are a potential source of such stress.

With the development and deployment of high performance and terrain-following tactical aircraft, operational crew are exposed to high G onset rates and dynamic acceleration environments with a significant frequency content below

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1 Hz for extended periods of time (7, 8). While cardiovascular responses to step acceleration loadings, "sustained acceleration," (9-11) and time-dependent acceleration loadings above 1.5 Hz, "whole body vibration," (12-14) have been extensively researched and documented, there is a lack of information concerning the speed with which the cardiovascular system can adjust to high G onset rates and to time-dependent acceleration loadings below 1 Hz.

During the past several years, our experiments have investigated the acceleration induced, pressure, flow and force disturbances which initiate peripheral vascular and cardiac mechanisms by neural, blood borne, and local feedback pathways. With the animal in a totally reflexive state, the frequency response characteristics of the intact cardiovascular system, as determined by heart rate, stroke volume, and total peripheral resistance, have been identified. The frequency response characteristics of the passive circulatory system (non-reflexive animal) have been established and compared to the animal in the reflexive state to evaluate the effectiveness of neural control mechanisms.

Although quantification of the frequency response of cardiovascular regulation in the reflexive animal is necessary and valuable, it does not however, provide frequency response information concerning specific efferent pathways which contribute to a particular response. To this end, we have developed a cardiac denervated animal preparation in addition to our normal preparation, and have conducted experiments to differentiate between central (i.e., cardiac) and peripheral (i.e., vascular) control mechanisms in the regulation of pressure and cardiac output during g_z acceleration. (See Section A.)

The second part of our effort deals with the acquisition and analysis of data for the development of describing functions for cardiac and vascular

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control mechanisms. During the present year, we have moved closer to the physiological sensors which respond to the acceleration induced pressure, flow and force disturbances and initiate the appropriate corrective action. To this end, we have made pressure measurements at the aortic arch, the right and left ventricles and at the carotid sinus level (both arterial and venous) in the same animal in a reflexive and later nonreflexive state. (See Section B.) These data will provide for the development of mathematical relationships or combinations of relationships between the pressure disturbances (input) and peripheral vascular resistance, heart rate and stroke volume changes (output). These describing functions are becoming more essential as efforts to model circulatory and respiratory responses (Dr. Collins, AFOSR Grant No. 76-2405) to simulated high speed aerial combat maneuvers become more sophisticated.

Lastly, we have consistently seen an increase in mean arterial pressure, from control values, during the time animals were exposed to the oscillatory acceleration loadings. This has been observed for both normal and cardiac denervated animals in both the reflexive and nonreflexive states; suggesting a nonautonomic neural response. As a result, we have investigated changes in circulating levels of arginine vasopressin (ADH), plasma renin activity and/or plasma volume changes and more recently have collaborated with Dr. M. Ziegler (an AFOSR contractor) to investigate changes in circulating norepinephrine. (See Section C.)

A. CARDIOVASCULAR RESPONSES OF NORMAL AND CARDIAC DENERVATED DOGS TO TIME DEPENDENT ACCELERATION STRESS

Cardiovascular regulation of acceleration-induced pressure and flow disturbances entails a complex pattern of afferent and efferent neural activity. The global nature of the stress in the levels applied invokes a response from both low and high pressure sensory areas as well as possible mechano-vestibular mechanisms. In this light, it was felt that the dual activation of both peripheral and cardiac efferent activity in response to acceleration stress would disguise the contribution from either mechanisms separately and for that reason a preparation was sought which would allow for delineation of these reactions. As a result, ~~we developed~~ a canine chronic preparation that included a surgically denervated heart thereby permitting a detailed analysis of the peripheral vascular contribution to barostatic regulation HAS BEEN DEVELOPED.

ANIMAL PREPARATION

Heart Denervation and Implant: Adult male and female mongrel dogs of ~20 kg body weight were used as animal subjects in this study. The principles of laboratory care outlined by the National Society for Medical Research were rigorously observed.

The surgical procedures for the chronically instrumented preparation were performed aseptically in the animal care facilities of the Wenner-Gren Research Laboratory at the University of Kentucky. Thoracic implantations were made through an incision in the left fourth intercostal space, with the animal under sodium pentothal anesthesia and on artificial positive pressure breathing.

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The procedures for total surgical cardiac denervation which we are now using differ from those reported in our earlier work in that only a single left thoracotomy is required, rather than the original 2-stage procedure. The key to the success of the operation is that the efficacy of the denervation be confirmed prior to closure of the animal's chest by demonstrating the complete absence of change in atrial and ventricular contractile force and heart rate during stimulation of the left and right thoracic vagi and left and right stellate ganglia, all of which can be visualized through a left thoracic incision. The essence of the operation is to interrupt all small nerves coursing towards the heart by completely dissecting around the great arteries, particularly the pulmonary artery, and the right and left superior pulmonary veins. The superior vena cavae was also dissected free from surrounding connective tissue and the azygous vein tied and transected.

Before closing the chest, a full range of instrumentation was also implanted. After dissection from its attachments, the base of the ascending aorta was reinforced with a nylon curtain material to stimulate fibrotic growth and thereby prolong survival and enhance fixation of an electromagnetic flow transducer (Zepeda Instruments) to the vessel wall. A left ventricular pressure transducer (Konigsberg Instruments, P-5) was placed through the apex of the heart, to project 1 cm into the left ventricular chamber. In addition, a cannula was placed in the right atrium for the administration of drugs.

EXPERIMENTAL PROTOCOL

On the day of the experiment, the animal was tranquilized with an intramuscular injection of Innovar Vet at .075 cc/kg. Piezoelectric manometer-tipped

catheters (Millar PC 350, 5 French) were placed, under local anesthetic, in the right and left ventricles via small branches of a main femoral vein and artery, respectively. The arterial Millar gauge was used to calibrate the implanted Konigsberg gauge and then retracted into the aorta, just outside the aortic valve, to measure arterial pressure. The animal was maintained in a lightly tranquilized state for the duration of the experiment with serial injections of Innovar (0.5 cc/hr) administered through the right atrial cannula.

The measured physiological variables included aortic pressure and flow, left and right ventricular pressure and heart rate. On-line, digitally calculated variables included beat-by-beat stroke volume, cardiac output, peripheral vascular resistance, maximum dp/dt, and the pressure difference from the aorta to the right atrium.

Procedure for Autonomic Blockade: In order to delineate the neural and nonneural components of the measured cardiovascular responses to acceleration, a pharmacologically-induced total autonomic blockade was used to inhibit adrenergic and cholinergic activity at the effector site, thus removing normal reflex barostatic action.

The total autonomic blockade for the proposed study consisted of the alpha adrenergic blocker phenoxybenzamine (Dibenzyline) at 20 to 30 mg/kg administered over an hour, beta blockade with propranolol (Inderal) at 1 to 2 mg/kg over approximately ten minutes, and cholinergic blockade with atropine (Atropine Sulphate) at 0.1 to 0.2 mg/kg over approximately five minutes. The efficacy of the blockade was tested and verified by a comparison of systemic responses to specific agonists given prior to blockade, following blockade and then

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again at the conclusion of the blocked acceleration sequence. These consisted of a 50 µg/kg bolus of phenylephrine (Neosynephrine) to test the alpha blockade and a 0.5 µg/kg bolus of isoproterenol (Isuprel) to test the beta blockade. If heart rate showed evidence of reflexive parasympathetic activity (i.e., a decrease following phenylephrine) the atropine dosage was supplemented.

Test Sequence: The test sequence and experimental conditions were the same as in the previous years to allow for correlation of the experimental results. The sequence consisted of $\pm$ $2g_z$ sinusoidal acceleration from .005 to 0.3 Hz starting at the low frequency and moving to the next higher frequency at 3 to 4 minute intervals without stopping the centrifuge. Previous years' studies indicated that this protocol allowed steady state conditions to develop more rapidly than did a protocol which stopped the centrifuge between frequencies. The sinusoidal series of tests was followed by a step input series consisting of a 3 minutes each from $+2g_z$ to $-2g_y$ to $-2g_z$ to $+2g_y$ to $+2g_z$ to $-2g_z$ to $+2g_z$ and back to $-2g_y$. The first 4 inputs were produced by 90° rotation of the platform while the centrifuge is producing 2g radial acceleration. The last 2 inputs were produced by a 180° rotation each.

RESULTS

Selective cardiac denervation appeared to change the control state of these animals very little as illustrated in Table 1. Reflexive aortic pressure was slightly reduced as were the arterial-to-venous pressure difference and peripheral resistance, while cardiac output, stroke volume and heart rate were slightly elevated. Total autonomic blockade reduced aortic pressure in cardiac denervated dogs (-30%) to a greater extent than that of normal dogs (-18%) through an increased reduction in both peripheral resistance and cardiac output.

NORMAL ANIMALS (8)

	Mean Aortic Pressure mmHg	Arterial To Venous Pressure Difference mmHg	Peripheral Vascular Resistance mmHg/(L/min)	Cardiac Output L/min	Stroke Volume ml	Heart Rate b/min
REFLEXIVE ± SEM	95.1 ±6.3	99.4 ±6.3	49.2 ±4.0	2.12 ±.10	23.8 ±1.4	89.0 ±8.2
NON-REFLEXIVE ± SEM	77.8 ±11.9	80.2 ±14.5	39.3 ±5.7	2.06 ±.20	15.9 ±1.4	129.7 ±5.9

CARDIAC DENERVATED ANIMALS (8)

	Mean Aortic Pressure mmHg	Arterial To Venous Pressure Difference mmHg	Peripheral Vascular Resistance mmHg/(L/min)	Cardiac Output L/min	Stroke Volume ml	Heart Rate b/min
REFLEXIVE ± SEM	89.5 ±3.4	97.9 ±2.7	43.2 ±3.7	2.35 ±.19	25.4 ±1.3	92.5 ±5.6
NON-REFLEXIVE ± SEM	63.9 ±4.5	66.3 ±4.5	33.2 ±3.1	2.08 ±.16	16.2 ±1.5	128.8 ±5.9

Table 1. Pre-acceleration control values for 8 normal and 8 cardiac denervated dogs in both the reflexive and non-reflexive (following total autonomic pharmacological blockade) state.

The reflexive response of the cardiac denervated dogs to acceleration stress was however quite different from that of the reflexive, normal dog's response. Where the reflexive, normal animal was found to be able to minimize aortic pressure oscillations in the low frequency range (first column, Figure 1), with an in-phase increase in peripheral vascular resistance, the reflexive, cardiac-denervated animals were all found to have much larger oscillations in aortic pressure (Figure 2). Surprisingly, these oscillations were even greater than the oscillations seen in the nonreflexive animals, either normal or cardiac denervated.

A comparison of the oscillatory aortic pressure response between denervated and normal dogs is shown in Figure 3 for each group in both the reflexive and the nonreflexive state. The nonreflexive response for both groups was quite similar, with oscillations of the order of 50 to 55 mm Hg at the lowest frequencies tapering off to 20 to 30 mm Hg oscillations at the highest frequencies. That both groups of animals had the same nonreflexive response indicated that their nonneural components of the responses to acceleration stress were the same, and therefore comparison of the groups' reflexive states was reasonable. The reflexive normal oscillations were minimal at the lowest frequencies, about 35 mm Hg, peaking in the middle frequency range at about 55 mm Hg and tapering off like the nonreflexive animals to about 35 mm Hg at the highest frequencies. In contrast, the reflexive cardiac denervated pressure oscillations were quite large, about 70 mm Hg across the low to middle frequency range, tapering sharply off to 20 mm Hg at the highest frequency.

The maximum and minimum values of aortic pressure (from which the difference values above were taken) are shown in Figure 4 for both reflexive (i.e., non-blocked) normal animals and reflexive cardiac denervated animals across the

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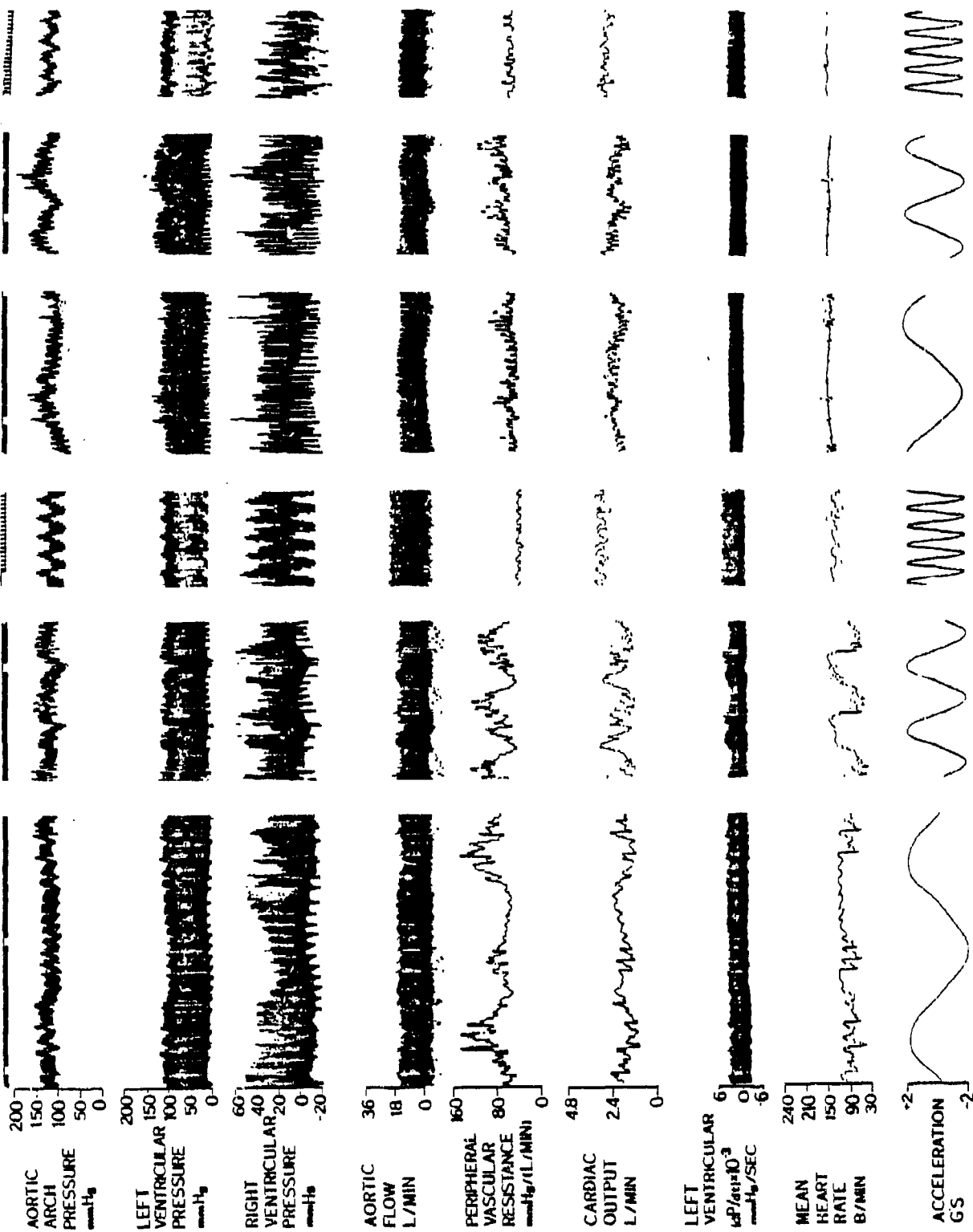
Figure 1 Reflexive and non-reflexive cardiovascular responses of a sedated, normal dog during sinusoidal ±2 g_z whole body acceleration. Traces 5 and 6 are one-beat-delayed, digitally calculated variables.
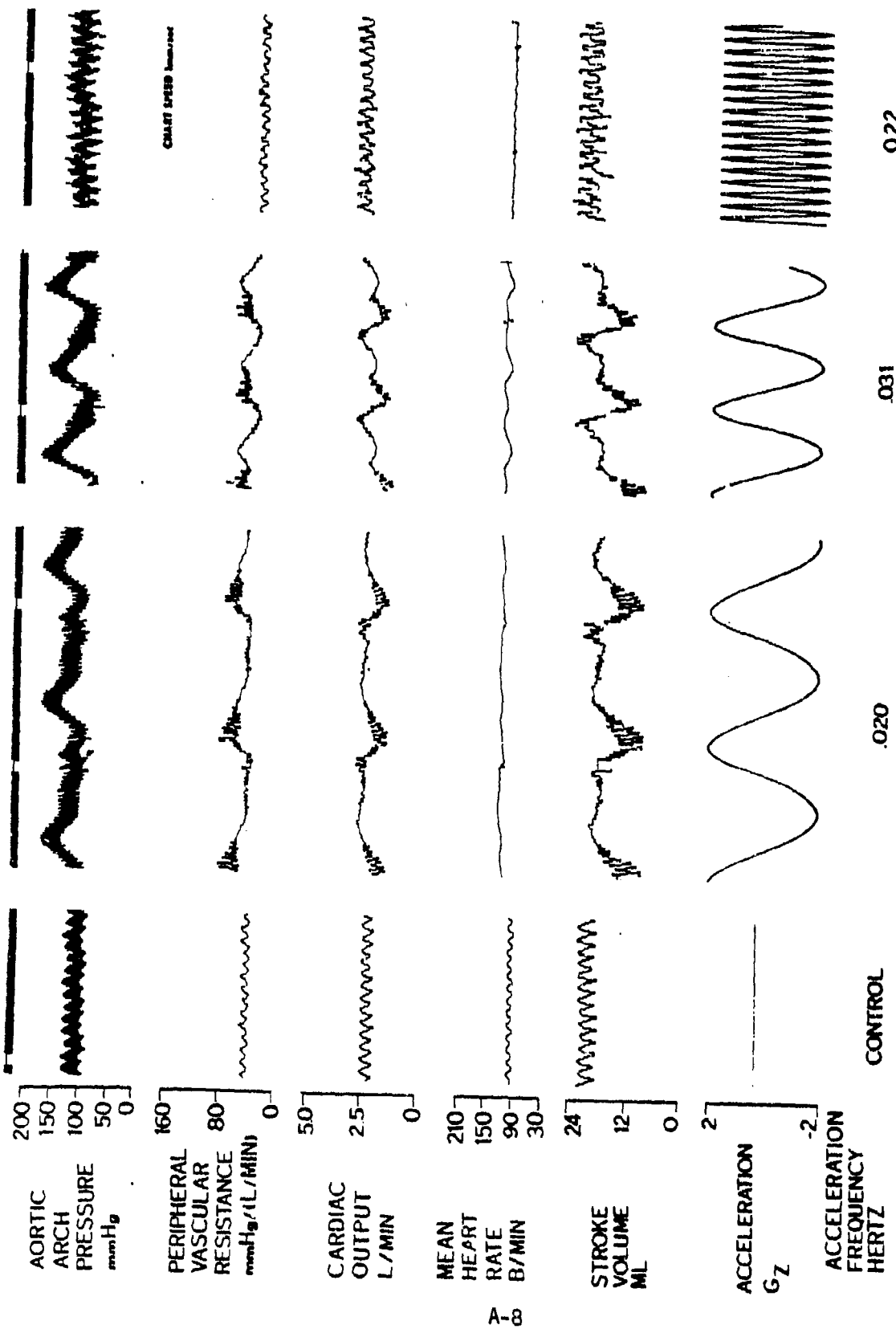
Figure 2 Reflexive cardiovascular responses of a sedated, cardiac denervated dog during sinusoidal ±2 gz whole body acceleration. Traces 2, 3, 4 and 5 are one-beat-delayed, digitally calculated variables.
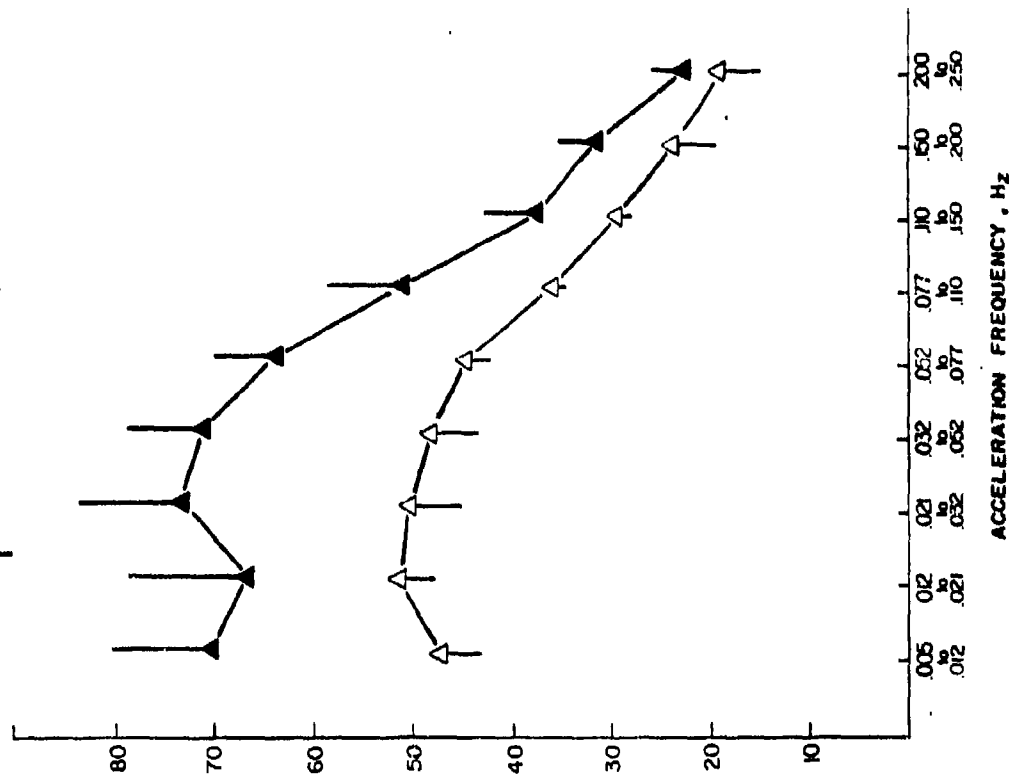
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AORTIC PRESSURE OSCILLATIONS

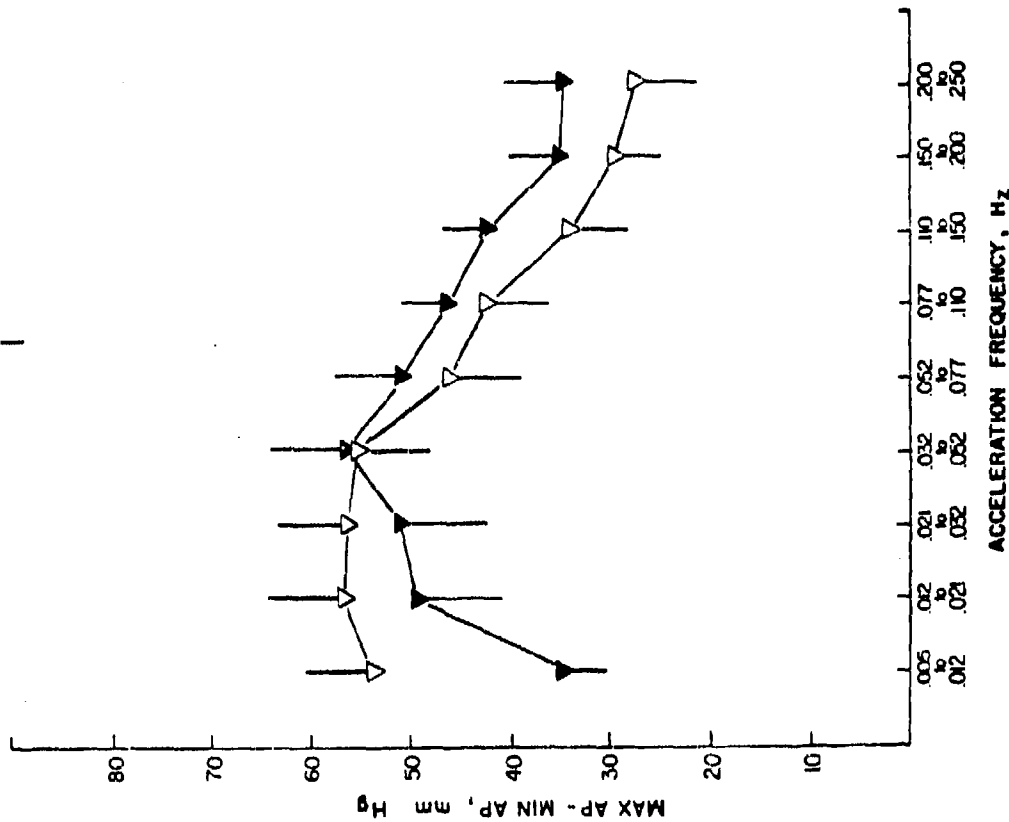Figure 3 Comparison of the magnitude of oscillations in aortic pressure across the frequency range studied for the group of normal animals (both reflexive and non-reflexive) and the group of cardiac denervated animals
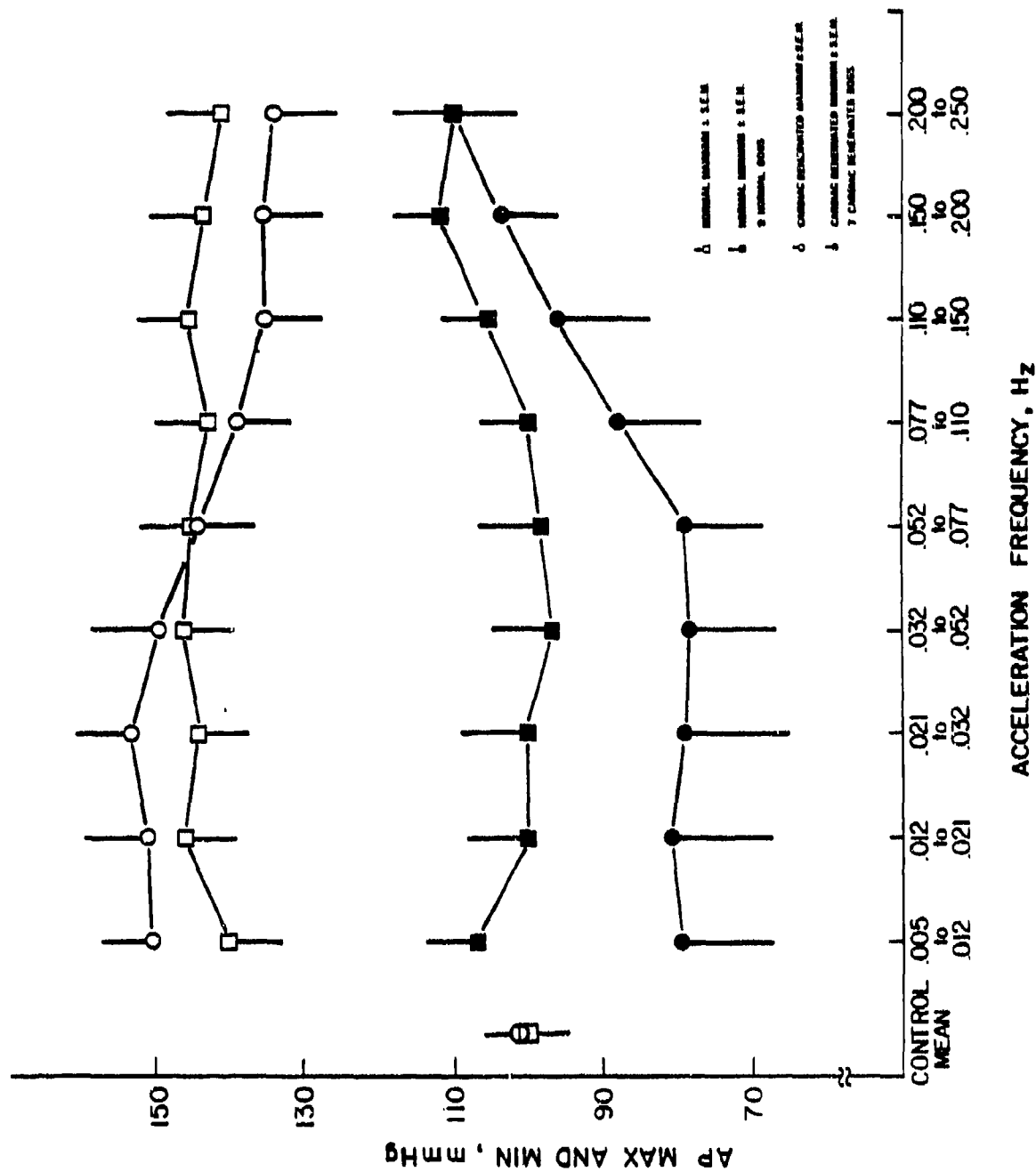
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Figure 4 Control values and maximum and minimum values of mean aortic pressure are shown for reflexive (unblocked) normal and cardiac denervated dogs across the frequency range studied

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frequency range studied. With $-2g_z$ (blood to the head), aortic pressure increased to about the same values (about 140 mm Hg) in both groups of animals, at all frequencies. With $+2g_z$ however, the cardiac denervated animals dropped to lower pressure than did the normal animals, about 80 mm Hg as compared to about 100 mm Hg across the low to mid-frequency range. Peripheral vascular resistance and cardiac output components of the oscillations in aortic pressure were examined in order to determine the mechanisms involved in the discrepancy between the responses of the two groups of animals.

An increase in peripheral resistance occurred with both + and $-g_z$. We chose to examine the major component, the $+g_z$ component. With $+2g_z$, the normal animals increased peripheral resistance to about 85 mm Hg (L/min) at the lowest frequencies, tapering off sharply to about 55 mm Hg (L/min) at the highest ones, Figure 5. The cardiac denervated dogs, however, while also reaching 85 mm Hg (L/min) at the lowest frequency, tapered off more gradually to about 65 mm Hg (L/min) at the highest frequency. Since in cardiac denervated animals, the greater decrease in aortic pressure in response to $+g_z$ was associated with either the same or slightly higher values of peripheral resistance than those in the normal dogs, the difference must lie in the values of cardiac output.

Maximum and minimum values of cardiac output for both groups of animals are shown in Figure 6. In response to $-2g_z$ both groups of animals increased cardiac output to about 2.5 L/min at the lower frequencies, rising steadily to about 3.3 L/min at the higher frequencies. In response to $+2g_z$, however, there was a significant difference in the two groups, with the normal animals decreasing to about 1.5 L/min while the cardiac denervated animals decreased to about 1.0 L/min.
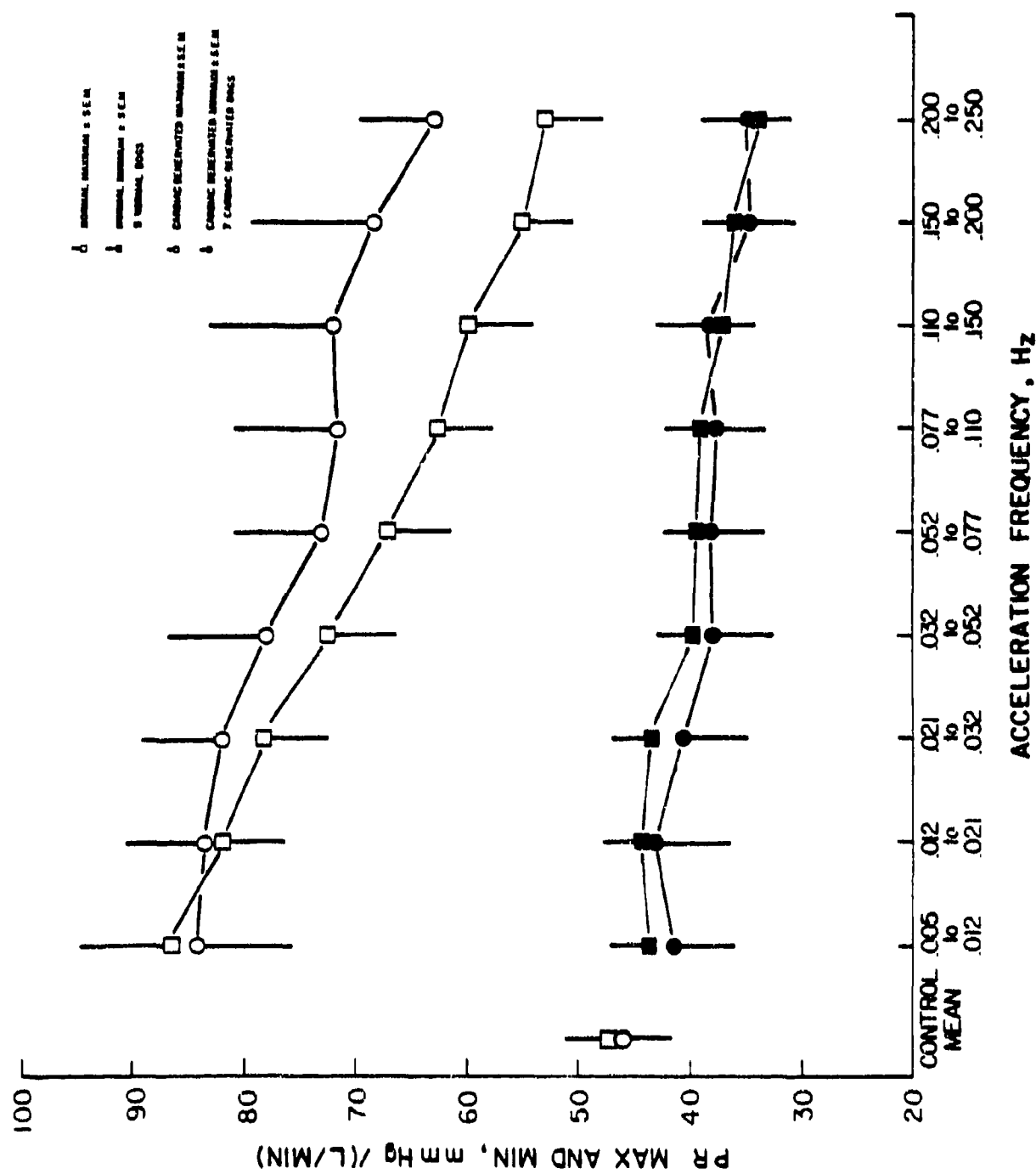
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Figure 5 Control values and maximum and minimum values of peripheral resistance are shown for reflexive (unblocked) normal and cardiac denervated dogs across the frequency range studied
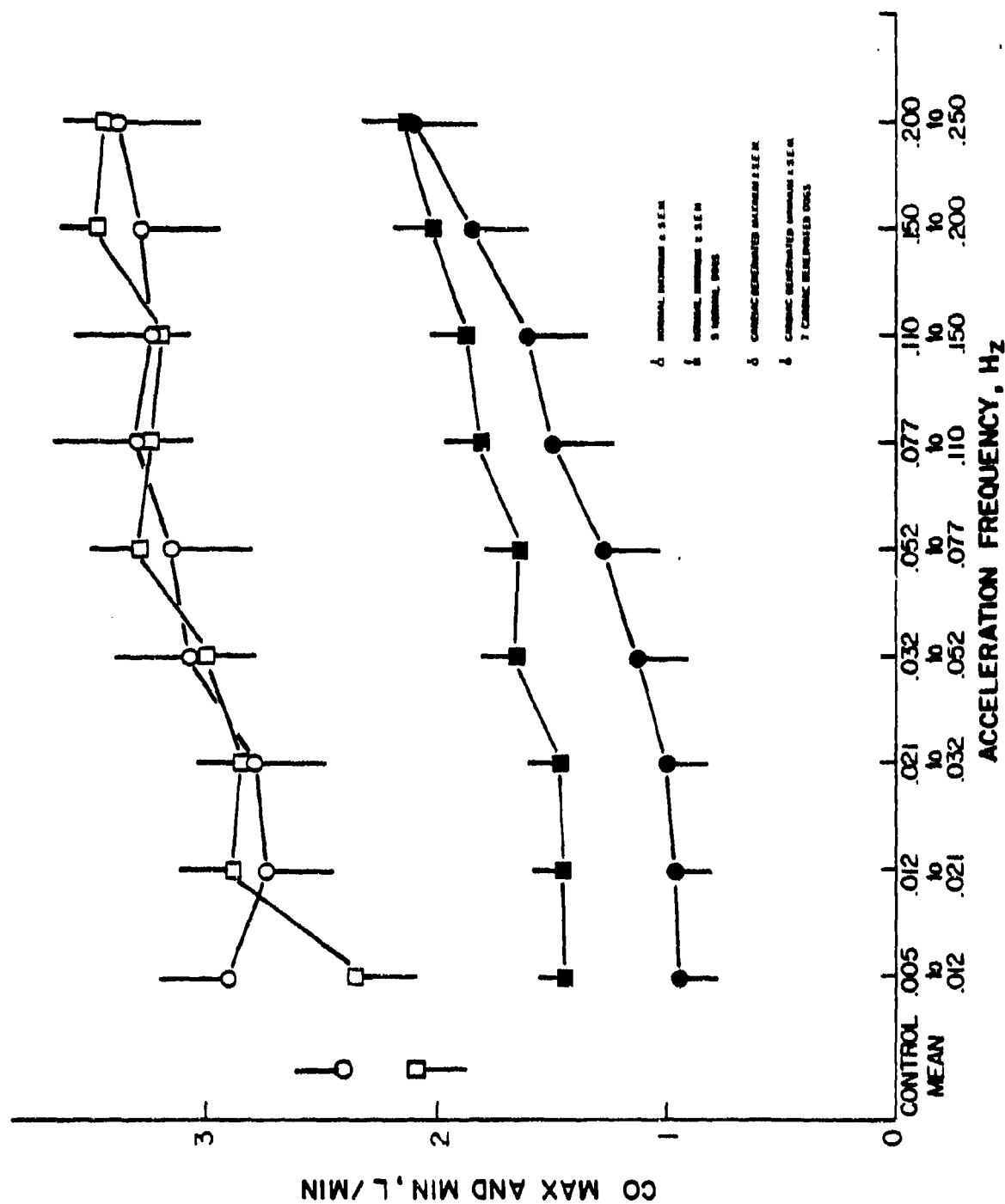
Figure 6 Control values and maximum and minimum values of cardiac output are shown for reflexive (unblocked) normal and cardiac denervated dogs across the frequency range studied

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The mean values of aortic pressure in both groups behaved similarly across the frequency range; from a control level of about 90 mm Hg, mean aortic pressure rose about 30 mm Hg with the onset of acceleration and remained at the same level across the test and for several minutes into recovery before returning to control levels. Mean values of peripheral resistance and cardiac output were distinctly frequency dependent. At the lowest frequency, mean peripheral resistance was at its maximal value with mean cardiac output at its minimal value; mean peripheral resistance then decreased steadily while cardiac output increased across the frequency range. The constantly elevated level of mean aortic pressure noted above, therefore, resulted from increased mean peripheral resistance at the low frequencies and increased mean cardiac output at the high frequencies.

DISCUSSION AND CONCLUSIONS

The cardiovascular response of tranquilized dogs to whole-body, sinusoidal, $\pm 2g_z$ acceleration across the frequency range of .005 to 0.3 Hz was examined. Two groups of animals were studied in two states each. A group of normal animals was studied first in the reflexive, unblocked state and again following total autonomic blockade. The second group, which had undergone selective cardiac denervation, was also studied in the reflexive, unblocked state and again following total autonomic blockade. The blocked studies were to quantify the nonneural pressure and flow disturbances which presumably the unblocked dog attempted to regular via cardiac and peripheral mechanisms. The blocked studies served another purpose also, they provided a state in which to compare the responses of the two groups of animals: normal vs. cardiac denervated. In

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the blocked state, with all autonomic efferent activity blocked, an identical response in the magnitude of oscillations in aortic pressure between the two groups indicated similar nonneural pressure disturbances to both groups of animals. A difference in the unblocked response, therefore, represented a difference in regulatory activity between the two groups in response to a common stimulus.

A large difference in the low frequency aortic pressure response with peak-to-peak oscillations of 70 mm Hg in the cardiac denervated dogs as opposed to 35 mm Hg for normal animals, was the most obvious discrepancy in the two groups' responses. This difference being in the magnitude of the drop in pressure in response to the $+2g_z$ portion of the cycle. At the lower frequencies during $+2g_z$, the drop in aortic pressure was much less in the normal dogs than in the cardiac denervated animals. Both groups responded with comparable increases in peripheral resistance, but the cardiac denervated dogs were unable to maintain cardiac output at the same level as did the normal dogs. An examination of the heart rate and stroke volume components of cardiac output showed that, at least at the lowest frequencies, this difference was due principally to differences in stroke volume. There were changes in heart rate in many of the cardiac denervated animals, but it was markedly reduced when compared to the normal animals. It is postulated that these changes in heart rate were a direct result of increased and decreased stretching of the S-A node due to the oscillatory changes in venous return, a question that can be studied only by measuring changes in heart dimensions.

The inability of the denervated animals to maintain stroke volume at the lowest frequencies with only Frank-Starling and humoral mechanisms intact,

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implicates inotropic mechanisms as being critically important in maintenance of cardiac output under acceleration stress. However, since cardiac denervation is not specific for efferent activity alone and afferent signals are also ablated, the possibility of a cardio-cardiac reflex as an important mechanism in beat-by-beat regulation of stroke volume cannot be ruled out; nor can differences in venous return.

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B. PRESSURE CHANGES AT VARIOUS RECEPTOR SITES IN THE CIRCULATORY SYSTEM IN RESPONSE TO TIME DEPENDENT ACCELERATION STRESS

Experiments have been performed to provide data for the development of suitable input/output relationships for neurally-mediated cardiovascular responses to acceleration stress. In the same animal, pressure measurements were made at five locations simultaneously. Measurements were made in the aorta in the vicinity of the carotid sinus, in the jugular vein at the same level as the carotid sinus measurement, and the right and left ventricles with special emphasis on diastolic pressures. These measurements provide information about 1) the distribution of the acceleration-induced pressure disturbances on the arterial and venous sides of the circulation at important receptor sites, 2) acceleration-induced pre-load and after-load influences on left ventricular performance, 3) changes in the pressure gradient (carotid artery-jugular vein pressure) which drives blood flow across the brain under acceleration stress, and 4) the relative importance of the carotid sinus, aortic arch and right and/or left atria as sensors for efferent peripheral resistance and cardiac output compensatory adjustments to acceleration loadings.

METHODS

The implantation of the instrumentation, the acceleration protocol and the procedure for autonomic blockade are the same as those described in Section A, except that the animals were not cardiac denervated. In addition, on the day of the experiment and after tranquilization and under local anesthesia, a mid-line, cervical incision was made on the ventral surface of the dog's

neck. One of the common-carotid arteries (either left or right) was cleared of fascia to expose the cranial thyroid artery. The carotid pressure gauge was inserted through this branch of the carotid and tied in place 2 to 4 cm below the carotid sinus bifurcation. The gauge was placed in this manner to assure 1) a stable position in the dynamic centrifuge environment, 2) a patent carotid artery and 3) normal carotid sinus function, without irritations from the gauge. In a similar manner, another pressure gauge was placed in the jugular vein at the same level as the carotid artery gauge.

RESULTS

Examples of aortic arch, left and right ventricular, carotid artery, and jugular vein pressures and acceleration are shown in Figures 7a-d. These data are from a normal dog in the reflexive state exposed to acceleration frequencies of 0.0144 Hz (Figure 7a) and 0.0556 Hz (Figure 7b), and in the nonreflexive states to approximately the same acceleration frequencies (Figures 7c and d respectively).

The effectiveness of the cardiovascular system to regulate aortic pressure can be evaluated by comparing the aortic pressure trace in Figure 7a for the reflexive state with that in Figure 7c for the nonreflexive state. These responses are from the same animal for approximately the same acceleration frequencies. During the $-2g_z$ portion of the acceleration loading, consistently occurring, skipped heartbeats allow elevated aortic pressur during systole to drop to extremely low values during diastole. The effect of this mechanism, possibly mediated by the vagus, is to keep mean aortic pressure relatively constant. When the animal is in the nonreflexive state, Figure 7c, this
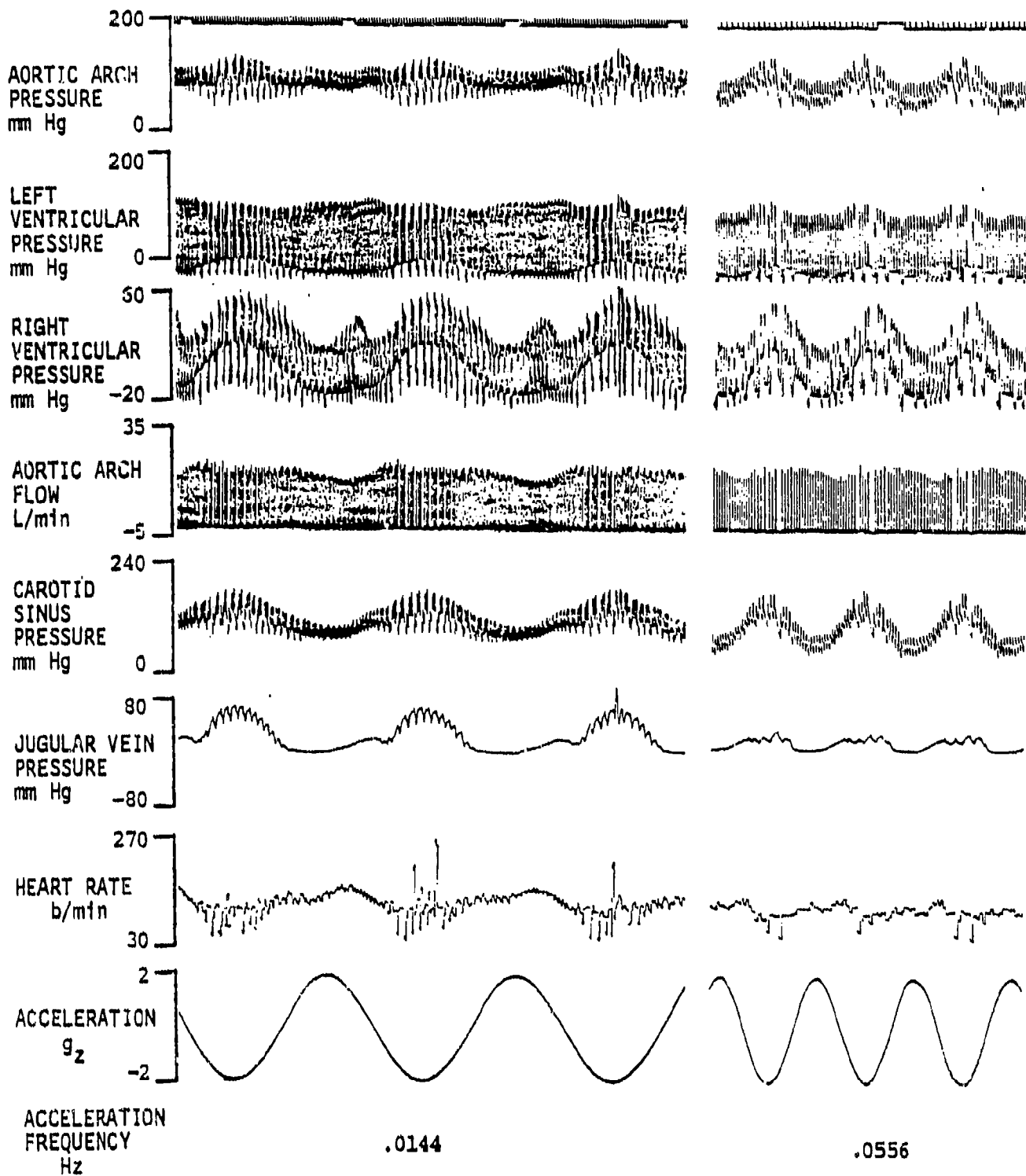
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Fig. 7 (a and b) Cardiovascular response of one animal in
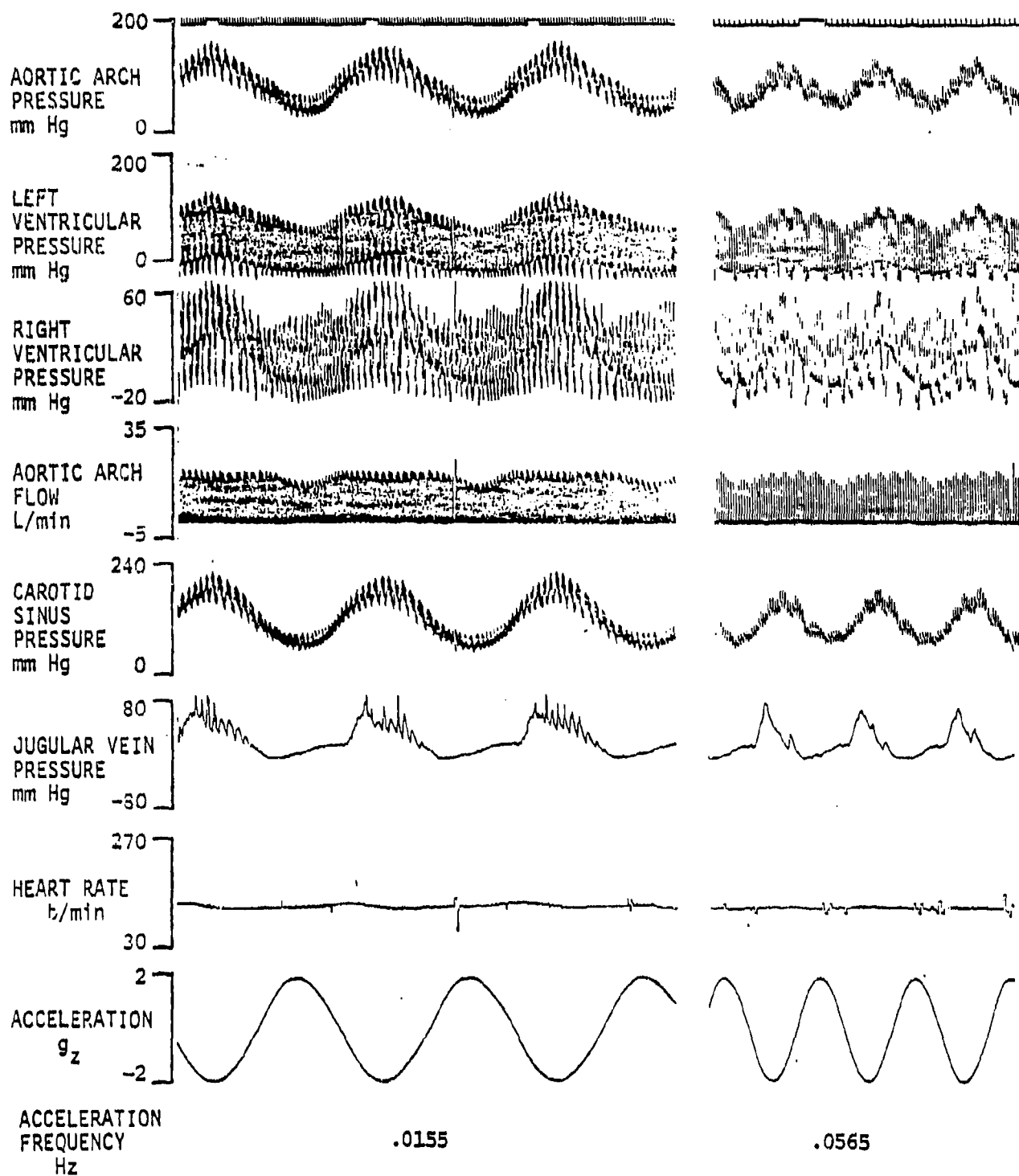the reflexive (unblocked) state to two acceleration frequencies

Fig. 7 (c and d) Cardiovascular response of one animal in the
non-reflexive (autonomically blocked) state to two acceleration frequencies

response is not evident. During the $+2g_z$ portion of the acceleration loading, reflexive mean aortic pressure (Figure 7a) did not drop as it did in the nonreflexive state (Figure 7c). In this case, maintenance of systolic pressure in the face of the $+2g_z$ acceleration results from an increased heart rate and cardiac contractility (reflected in dp/dt max. not shown). Elevated diastolic pressures resulted from the increased heart rate as well as increases in peripheral resistance (not shown).

For the faster acceleration frequency (0.0556 Hz), the oscillations in mean aortic pressure (Figure 7b) were larger than for 0.0144 Hz and were quite similar to the nonreflexive oscillations; suggesting that the regulatory mechanisms were not as effective in minimizing the disturbances at higher frequencies.

More detailed data of the pressure responses at the carotid sinus and aortic arch locations, (sites of well documented baroreceptors), as a function of acceleration frequency, are shown in Figures 8-11 for five animals in the reflexive state and three of the five animals in the nonreflexive state. Two of the five animals did not survive the nonreflexive tests, with cardiovascular failure occurring during the $-2g_z$ step input. The data set consists of the maximum and minimum pressure measured during a particular acceleration test; the amplitude of the pressure oscillations, i.e., the difference in maximum and minimum pressure; and the corresponding mean pressure during the test.

Following the initiation of the acceleration exposure, there is an overall stress response indicated by a 10 to 30 mm Hg increase in mean arterial pressure (Figure 8). The elevated mean pressure remains relatively constant across the frequency range. This pressor response was observed in both the reflexive and nonreflexive states.
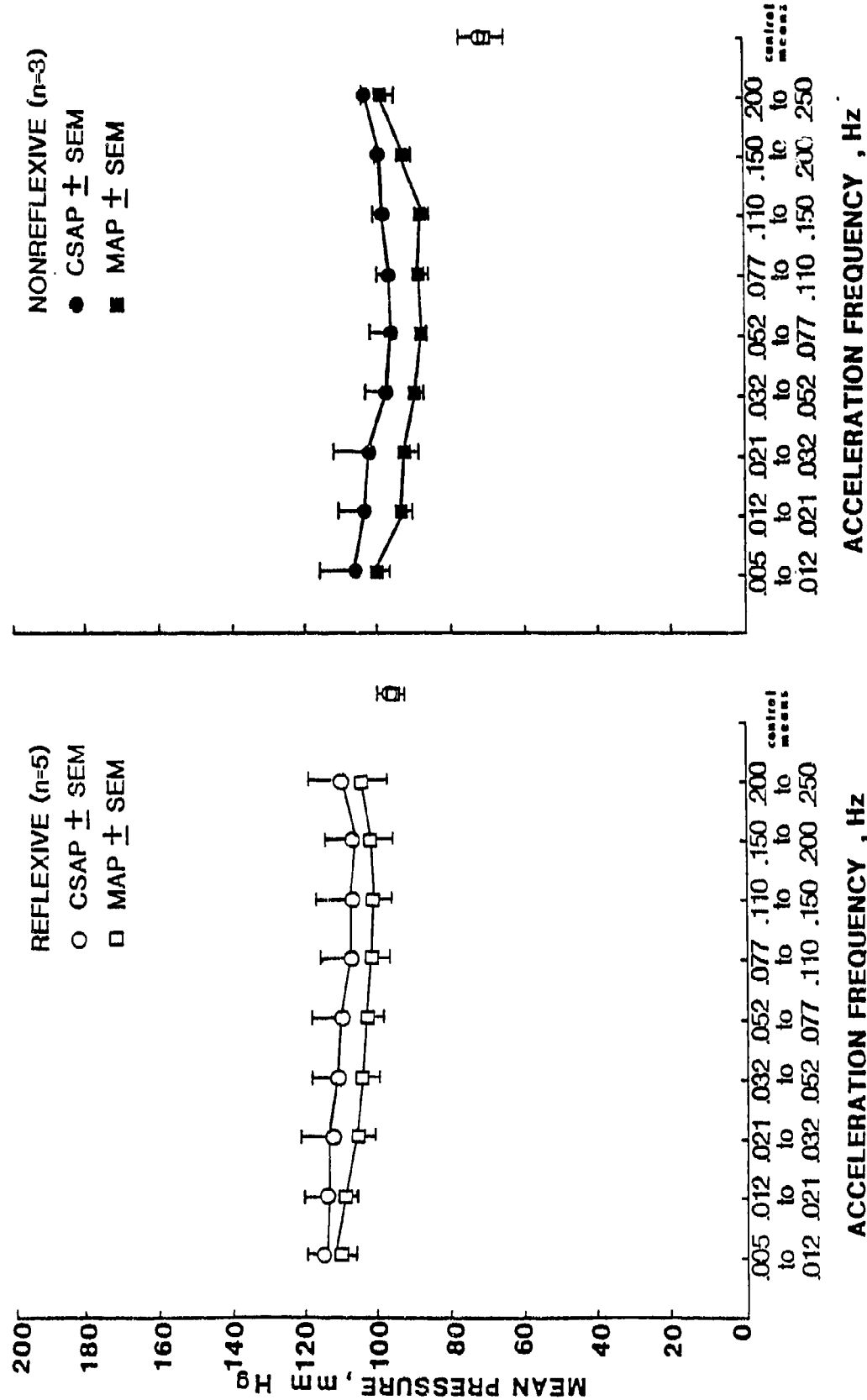
Figure 8 Mean aortic and carotid sinus pressures for a group of dogs in the reflexive (left) and nonreflexive (right) states across the acceleration frequency range studied.

For the animal in the nonreflexive state (Figure 10), the amplitude of the oscillations in arterial pressure was maximal at the lowest acceleration frequencies and then decreased with increasing frequency. For the reflexive state, the amplitude of the oscillations was small for the lowest frequencies. It increased with increasing frequency, reaching maximum values between 0.032 and 0.077 Hz and then decreased for higher frequencies. The oscillations in carotid artery pressure were from two to three times larger than those of the aortic arch for both states.

A comparison of the reflexive and nonreflexive states (Figure 11) indicates a significant decrease in the amplitude of the reflexive aortic pressure responses for frequencies below 0.012 Hz. For example, the 65 mm Hg oscillations which occurred when the animal was in the nonreflexive state were decreased to approximately 25 mm Hg when reflexive mechanisms were available for regulation. The large oscillations in aortic pressure observed in the nonreflexive state at the lowest acceleration frequencies resulted from the inability of the system to maintain blood pressure at <u>reflexive levels</u> during the $+2g_z$ portion of the acceleration loading (Figure 9). However, because control values for the reflexive and nonreflexive states were different, it may be more appropriate to compare responses to control levels. Viewed in this way, the main difference in the two responses resulted, not from a decreased pressure below <u>control values</u> for $+g_z$, but rather from the inability of the nonreflexive animal to lower aortic blood pressure during the $-g_z$ portion of the acceleration stress. That is, in the low frequency range where regulation is most effective, the maximum values of pressure were significantly greater <u>relative</u>

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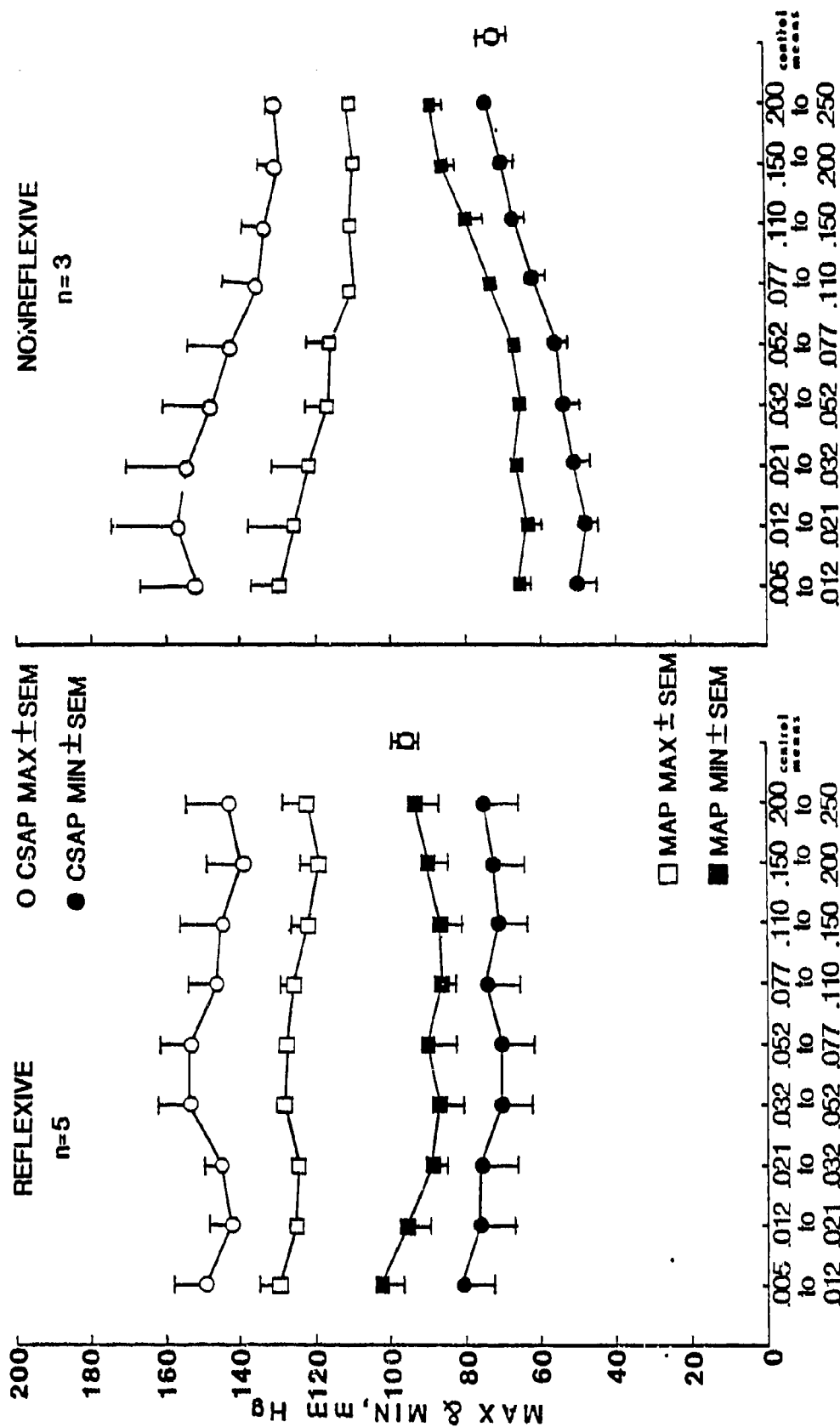
Figure 9 A comparison of maximum and minimum pressures seen by carotid sinus and aortic arch sensors for a group of animals studied in the reflexive (left) and nonreflexive (right) states across the frequency range shown.

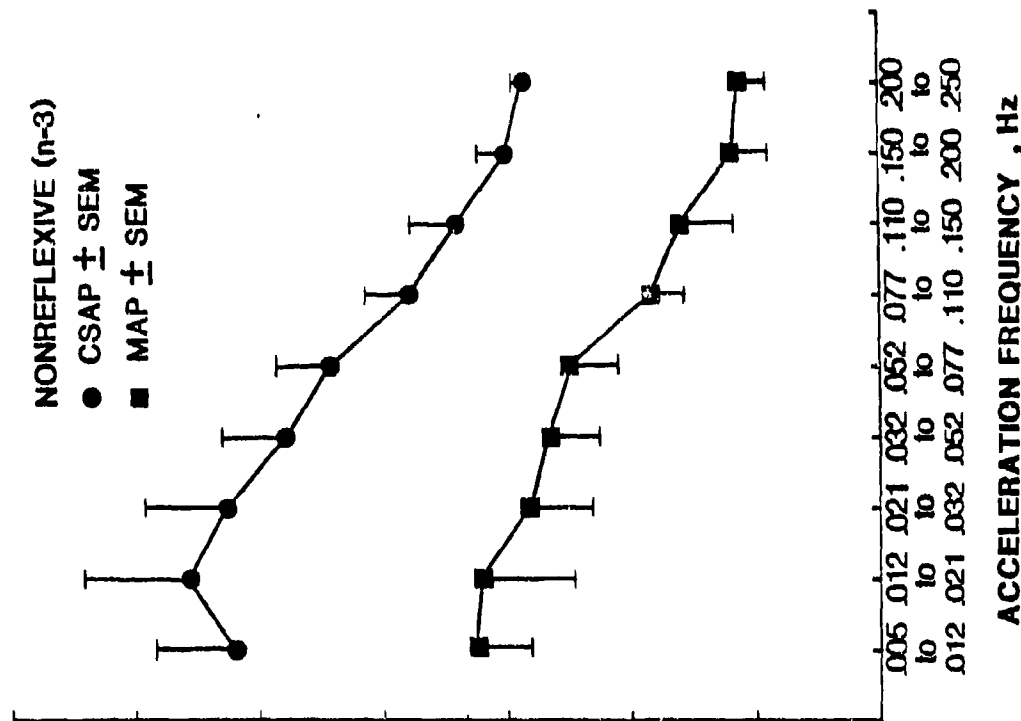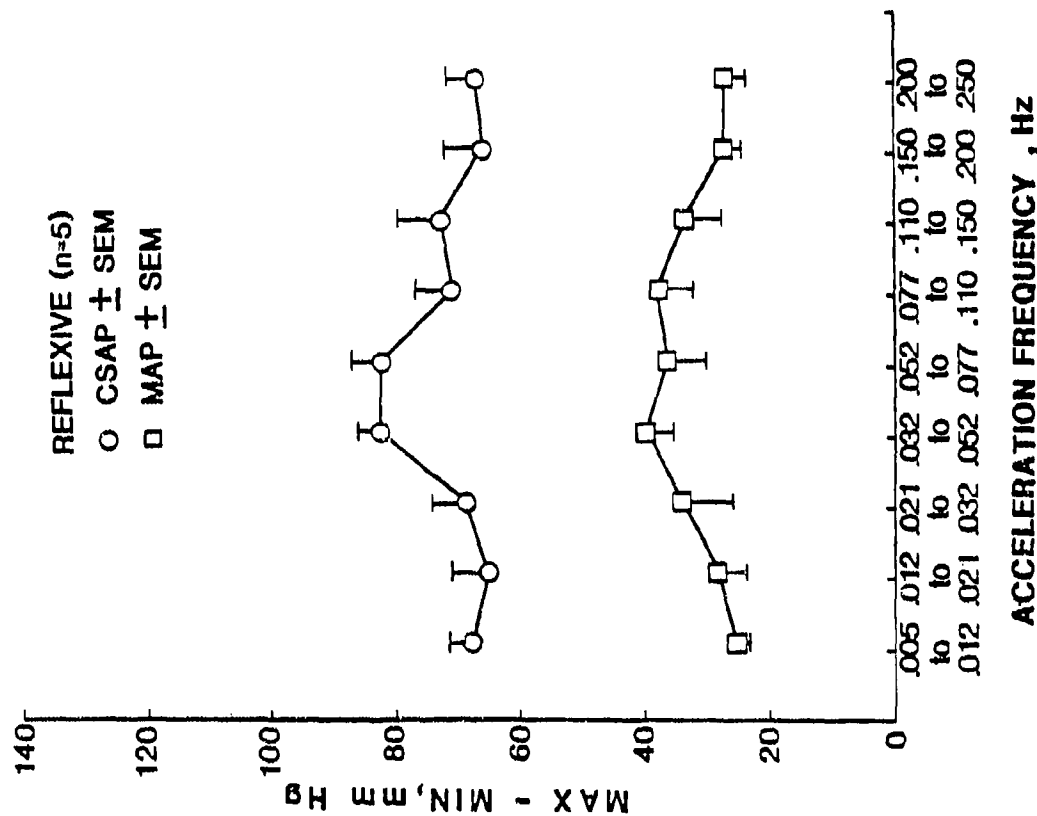Figure 10 A comparison of the magnitude of pressure oscillations seen by aortic arch and carotid sinus sensors for a group of animals studied in the reflexive (left) and nonreflexive (right) states across the frequency range shown.
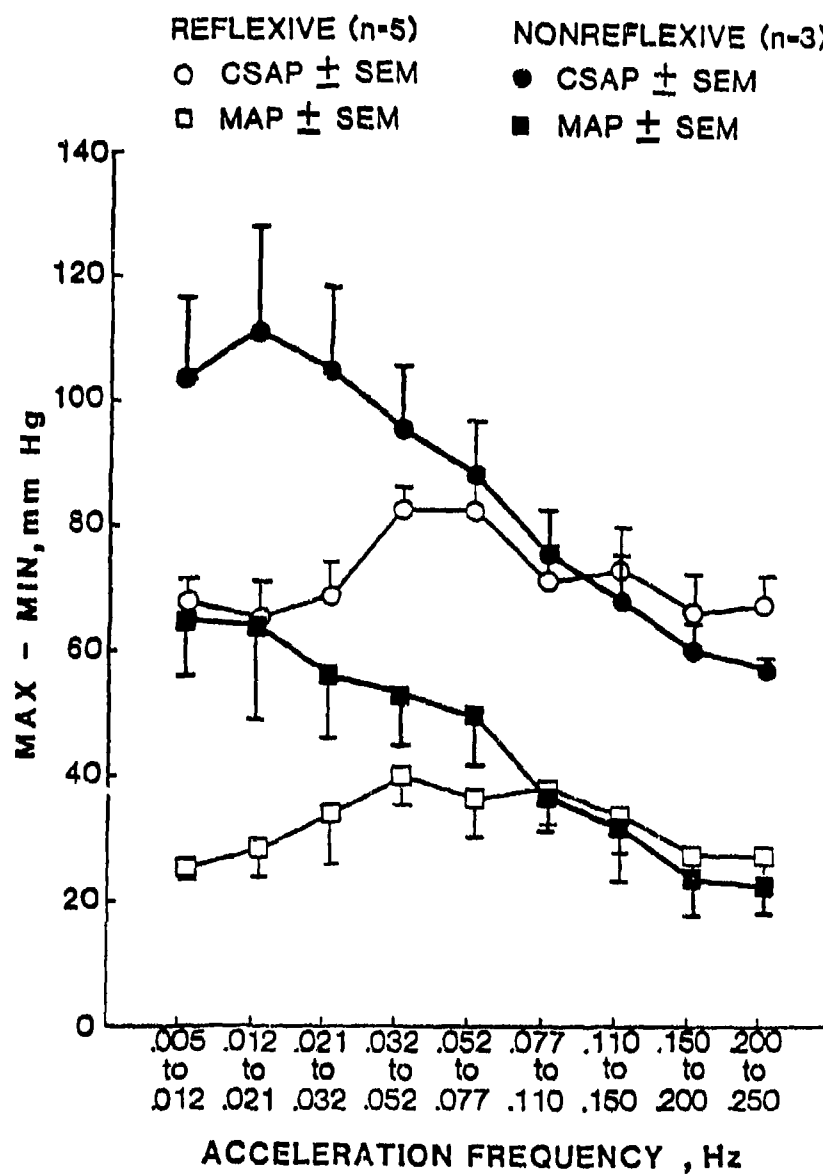
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Figure 11 Superposition of the magnitudes of oscillations seen by aortic arch and carotid sinus sensors for the reflexive and nonreflexive dogs of Figure 10.

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to control values for the nonreflexive state than they were for the reflexive state (Figure 9); the minimum values (due to $+g_z$) for both states, dropped to their respective control values. Regardless of the interpretation of the data, it does appear that the control values determine the degree to which aortic pressure drops during the $+2g_z$ portion of the acceleration loading.

Details of the pressure responses in the jugular vein and right atria (as indicated by right ventricular diastolic pressure) are shown in Figures 12-14 as a function of acceleration frequency. These data were analyzed in the same manner as that for the arterial side.

In the reflexive state, the mean value of diastolic right ventricular pressure was slightly elevated (not statistically significant) over the entire acceleration frequency range (Figure 12). For the nonreflexive state, mean diastolic right ventricular pressure remained unchanged from control. Mean jugular vein pressure increased above control values for both conditions with the largest increase occurring for the nonreflexive state.

The amplitude of the excursions in diastolic right ventricular pressure remained relatively constant across the frequency range for the animal in both the reflexive and nonreflexive states (Figure 14). The double amplitude of diastolic right ventricular pressure was approximately 9 mm Hg/G for the reflexive state and 12 mm Hg/G for the nonreflexive state. The amplitude of the excursions in jugular vein pressure was large for the lowest frequency and then rapidly decreased with increasing frequency for the reflexive state. In the nonreflexive state, the oscillations in jugular vein pressure remained elevated across the frequency range. This difference is a result of decreased jugular vein pressure during the $-2g_z$ portion of the acceleration stress for

B-11
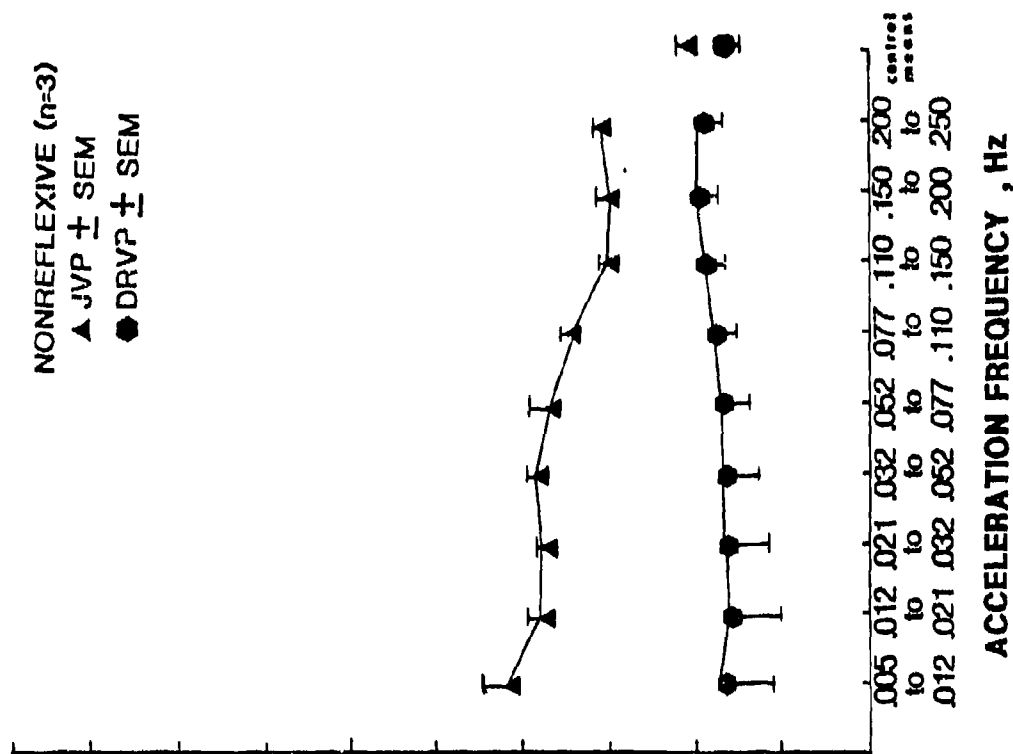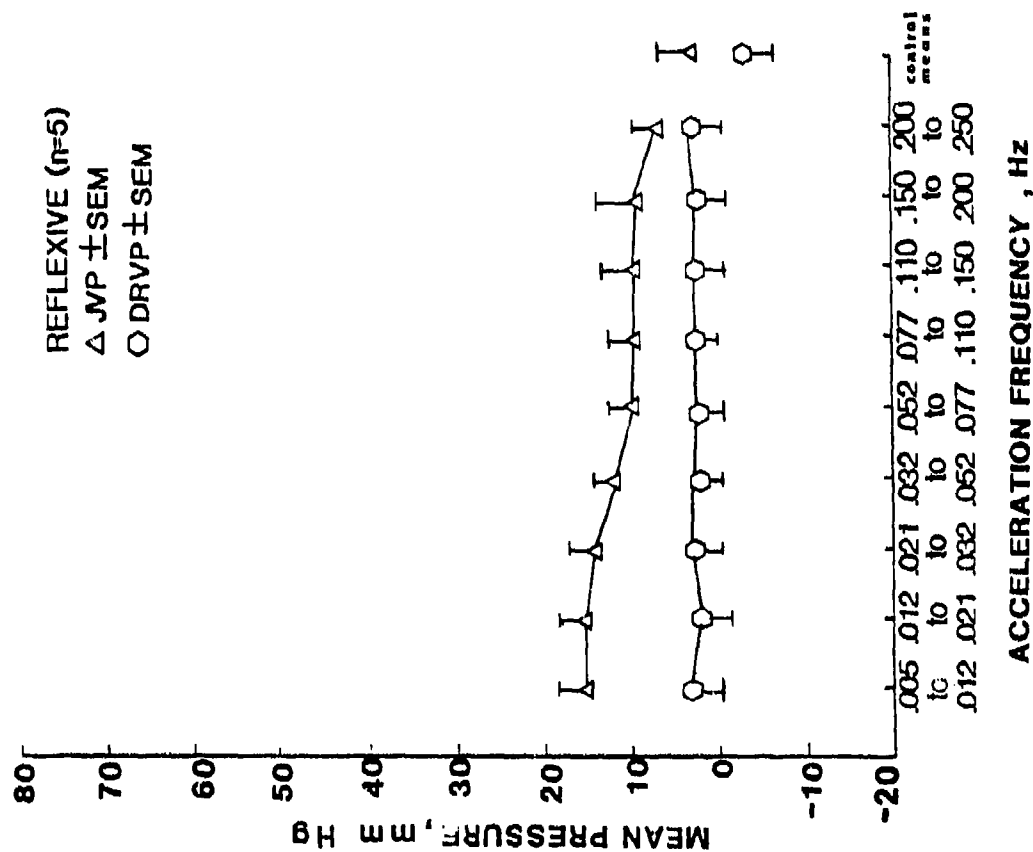
Figure 12 Mean jugular and diastolic right ventricular pressures for a group of dogs in the reflexive (left) and nonreflexive (right) states across the frequency range studied.

B-12
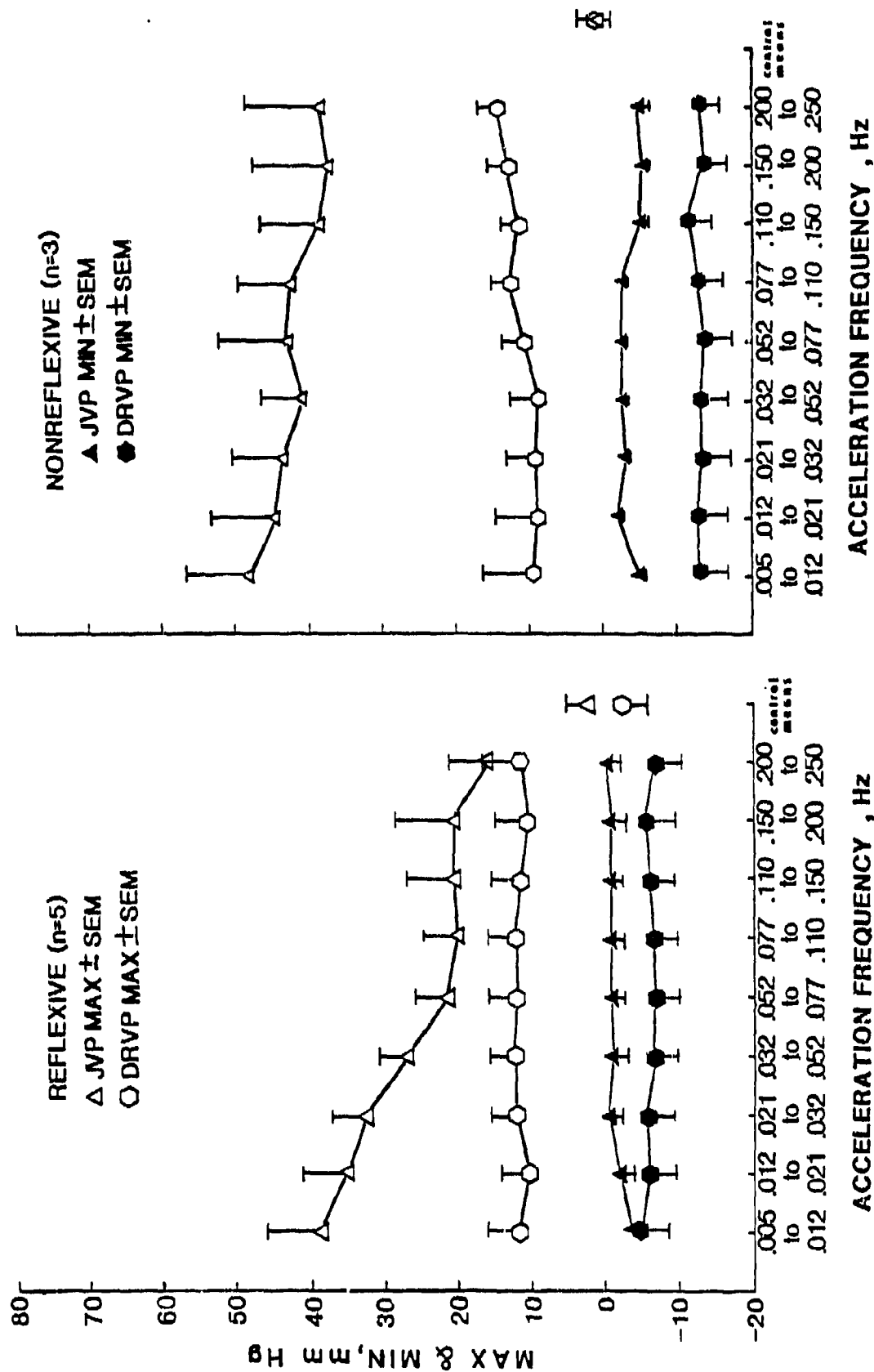
Figure 13 A comparison of maximum and minimum pressures in the jugular vein and the right ventricle (during diastole) for a group of animals studied in the reflexive (left) and nonreflexive (right) states across the frequency range shown.

B-13

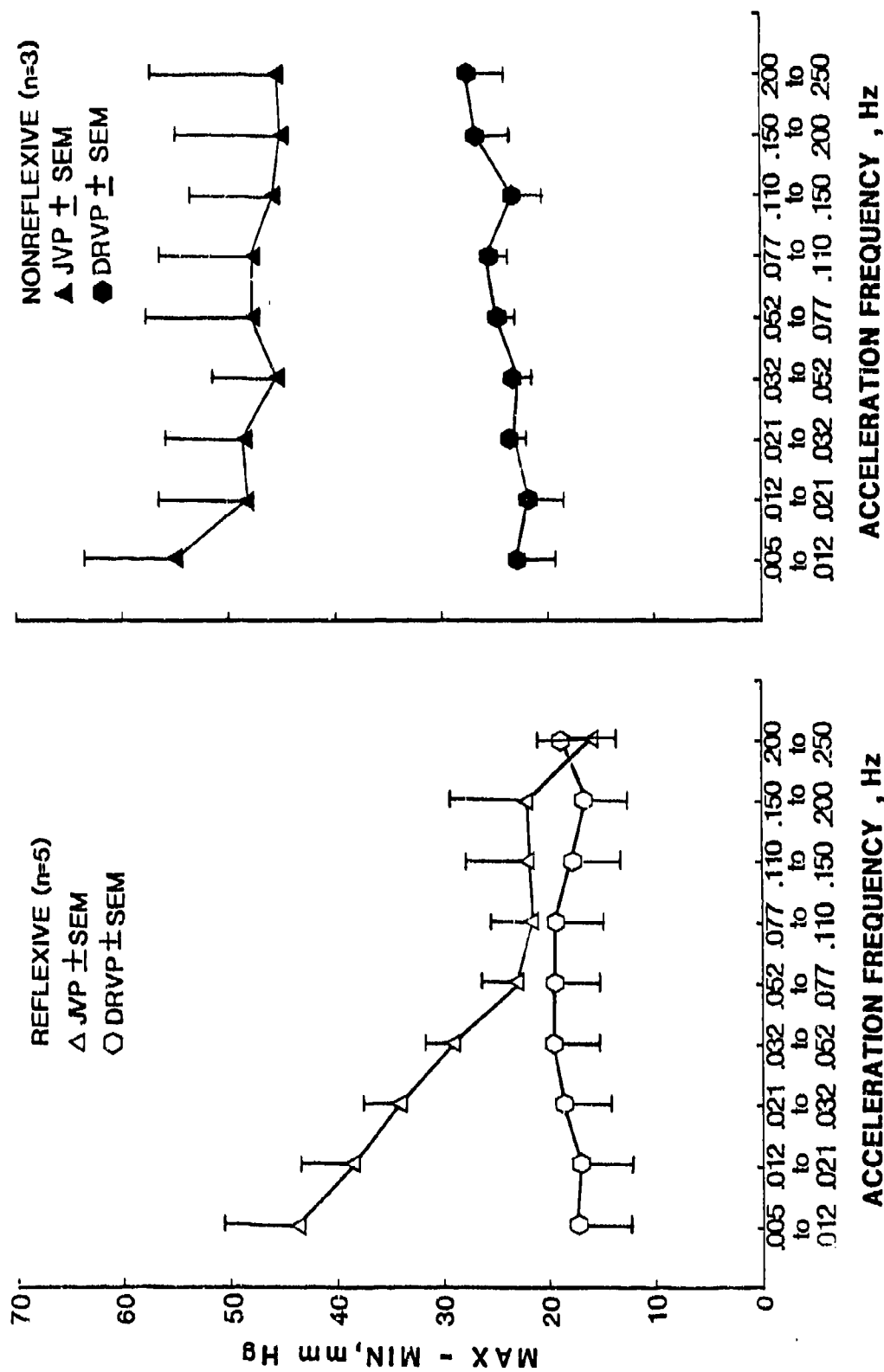Figure 14 A comparison of the magnitude of oscillations in pressure seen by the jugular vein and the right ventricle (during diastole) for a group of animals studied in the reflexive (left) and nonreflexive (right) states across the frequency range shown.

B-14

animals in the reflexive state when compared to their responses in the nonreflexive condition (Figure 13). The responses to the +2g_z portion of the acceleration stress were essentially the same.

Further analysis of the data such as carotid sinus - jugular vein pressure which is an indication of the pressure gradient across the brain are continuing (AFOSR Grant No. 80-0039) and will be reported in subsequent progress reports.

DISCUSSION

Although the present data must be viewed as preliminary, several observations can be projected at this time. One of the objectives of this study was to quantify the nonneural responses of the cardiovascular system to time dependent acceleration loadings. It is tempting to assume that the animal in the nonreflexive state also represents an approximation of the passive "hydraulic" circulatory system. The accuracy of this assumption, of course, depends upon blood borne hormonal and local regulatory mechanisms, which may not be muted by the pharmacological blockade used in these studies, and their response characteristics. For example, the lowest acceleration frequency used, 0.005 Hz, has a period of 200 seconds; possibly sufficient time for nonneural mechanisms to be effective. As the acceleration frequencies increase, the influence of the nonneural mechanisms in terms of dynamic regulation should be minimal because of their slow response characteristics. However, it is very likely that these mechanisms produce "dc" level responses over the length of time the animal is subjected to the acceleration stress. Evidence of this is suggested by the overall mean pressor response seen in the data of Figure 8. Even

B-15

with these considerations, however, it may not be unreasonable to assume that the animal in the nonreflexive state is a first approximation to the passive "hydraulic" circulatory system and that the nonreflexive responses in Figure 10 are primarily the acceleration induced disturbances at the carotid sinus and aortic arch baroreceptors. If so, these data may be used to develop open loop acceleration-to-pressure describing functions for driving models of the cardiovascular system under acceleration stress. From the data in Figure 10, the "passive" circulatory system appears to have a resonant frequency in the range of 0.012 to 0.021 Hz. Further experiments are especially needed at frequencies lower than 0.005 in order to define more precisely what appears to be a drop off in the amplitude for frequencies less than 0.012 Hz (Figure 10). It will also be necessary to ascertain whether this apparent decrease in amplitude is due to nonneural regulatory factors or is indeed a characteristic of the "hydraulic aspects" of the circulatory system.

The nonreflexive data of Figure 10 should serve as a basis for comparison with data from those performing model studies. Nonneural models of the cardiovascular system should show decreases in the acceleration induced arterial pressure disturbances with increasing frequency of constant amplitude acceleration above .021 Hz. The decrease in the half amplitude of the pressure disturbance should be roughly 0.5 mm Hg/g/milli Hz. The difference in the double amplitude of the "open loop" pressure input to the two baroreceptors should be approximately 20 mm Hg/g and stays relatively constant across the frequency range. This corresponds to an average hydrostatic column height between the aortic arch and carotid sinus receptors of about 11 inches which is consistent with the measurements made on the animals in this study.

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With the neural regulatory mechanisms intact, the resonant frequency of the system appears to be shifted from that of the nonreflexive system and occurs in the frequency range of 0.032 to 0.077 Hz (Figure 10). It appears that the neural regulatory mechanisms are "designed" to be the most effective below 0.032 Hz, the region where the nonreflexive oscillations were found to be greatest. For the higher acceleration frequencies, the nature of the passive "hydraulic" system is to minimize pressure disturbances with increasing frequency. The "weakness" in the system appears to be in the frequency range between 0.032 and 0.077 Hz; an acceleration frequency range where the "hydraulic" pressure disturbances are still relatively high and challenge the frequency response characteristics of the neural regulatory mechanisms. It is in this frequency range that the least protection is afforded by the neural regulatory mechanisms.

The responses of jugular vein pressure in the reflexive and nonreflexive states are interesting and confusing. It appears that the primary difference between the reflexive and nonreflexive responses in jugular vein pressure is due to a possible increase in venous volume during the nonreflexive state. This is suspected because of the significant drop in the nonreflexive control values of arterial pressure when compared to the reflexive state. There was also a correspondingly small increase in jugular vein pressure for the nonreflexive state. This very small increase in jugular vein pressure may represent a significant increase in volume available to the venous side. This fact coupled with the highly nonlinear nature of the venous system (i.e., one way valves and collapsible vessels) could explain the large oscillations in jugular vein pressure. Conversely, if less volume is available on the venous side for the

reflexive state, a more frequency dependent response could be anticipated such as that observed in Figure 14. Efforts to better understand these responses are being pursued under AFOSR Grant No. 80-0039.

C. NEUROHORMONAL COMPONENTS OF THE ACCELERATION INDUCED PRESSOR RESPONSE IN BOTH NORMAL AND CARDIAC DENERVATED ANIMALS

For the past several years, we have observed that the low frequency, sinusoidal acceleration used as a stressor in this study routinely produced an increase in aortic pressure, heart rate, peripheral vascular resistance and left and right ventricular (diastolic) pressures, and a decrease in stroke volume and cardiac output in Innovar-sedated dogs (Figures 4-6). This pressor response was evident within the first minute of the onset of centrifugation, persisted throughout the 30 minutes of the test period, appeared to be fairly independent of the frequency of acceleration, and remained for several (10 to 15) minutes following the end of the test period. In addition, it appeared to be independent of autonomic effector activity since it was common to both normal (reflexive) dogs and dogs in which sympathetic α, β and cholinergic activity had been pharmacologically blocked (nonreflexive dogs). The magnitude of the response significantly increased aortic pressure by approximately 20 mm Hg in reflexive dogs and by double that amount in nonreflexive dogs (Figure 15a).

A separate study was therefore initiated to quantify the response and its correlation with various neurohumoral mechanisms.

METHODS

The 21 animals used in this study were a random sampling of the normal and cardiac denervated dogs undergoing our normal acceleration protocol (see Animal Preparation and Experimental Protocol, Section A). Right atrial blood samples were withdrawn from these animals before, and within 3 minutes following, 30

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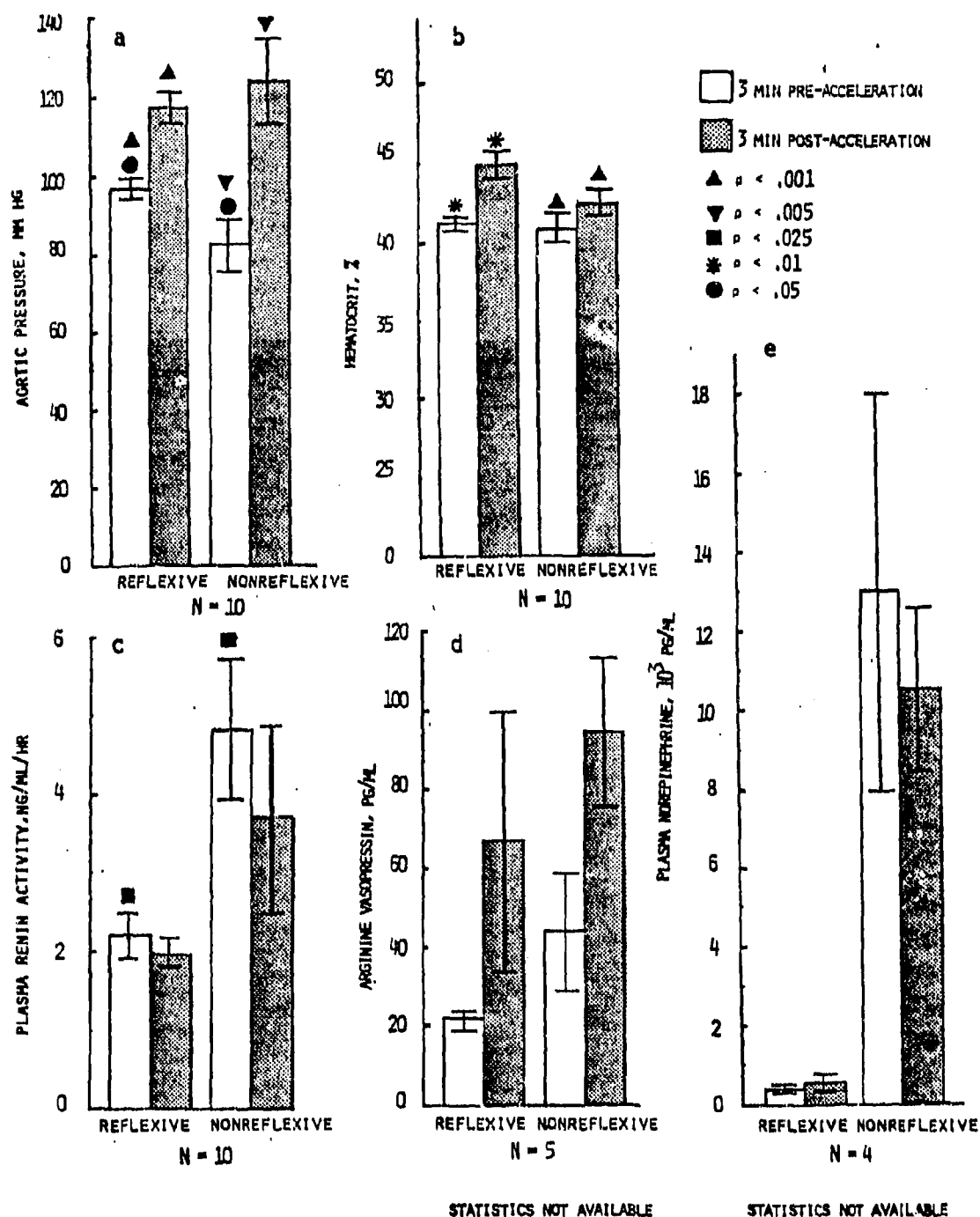
Figure 15 Aortic pressure and neurohumoral responses to 30 min. of low frequency acceleration stress for a group of animals in the reflexive and nonreflexive (following total autonomic blockade) states. The "repeated measures to the same subjects test" was performed to test for significant differences in control to test means for each state and to test for differences between control states.

minutes of sinusoidal acceleration stress. Pre and post acceleration samples were taken from the animal in both the reflexive state and following total autonomic blockade produced by intravenous infusion of propranolol (1 mg/kg) atropine (.1 mg/kg) and phenoxybenzamine (30 mg/kg). Each sample was analyzed for at least two of the following variables: hematocrit, plasma renin activity, plasma arginine vasopressin (ADH) activity, plasma norepinephrine levels and plasma volume. Subsequent analysis of these samples was performed by various laboratories chosen for their expertise in the analyses to be performed. Plasma renin activity was done by Dr. Theodore Kotchen of the University of Kentucky, Department of Medicine. Arginine vasopressin activity (and plasma osmolality) were determined by Dr. Gary Robertson of the Department of Medicine at the Indiana University Medical Center and, just recently, plasma norepinephrine levels have been determined by Dr. Michael Ziegler of the Departments of Pharmacology and Internal Medicine at the University of Texas, Medical Branch. Plasma volume was determined by the Evans blue technique (2 dogs) and by the RISA[131] technique (7 dogs) through the Department of Nuclear Medicine, University of Kentucky and hematocrit was done in our own laboratory. Results from the above tests are summarized below by variable, as well as in Figure 15 which includes a summary of aortic pressures at the time of the blood sample withdrawal.

RESULTS

Plasma volume as indicated by RISA[131] or hematocrit changes: In contrast to the other variables measured, plasma volume did appear to change with the animal preparation (normal vs. cardiac denervated). Results from the RISA[131]

and Evans blue determinations indicated plasma volumes of 1063 $\pm$ 205 ml (S.E.M.) in 5 normal animals with plasma volumes of 765 $\pm$ 86 ml (S.E.M.) in 4 cardiac denervated animals. Hematocrit (taken in this study as an inverse indication of plasma volume) was also elevated in 6 cardiac denervated (40.8 $\pm$ 1.4) as compared to 6 normal (37.4 $\pm$ 2.7) dogs.

Acceleration-induced changes in plasma volume as indicated by serial determinations following the original RISA[131] injection were not consistent in either normal or cardiac denervated dogs. However, plasma volume changes as indicated by hematocrit (Figure 15b) were evident with each acceleration test in both normal and cardiac denervated dogs. Since hematocrit increased significantly with acceleration indicating a decrease in plasma volume, other variables were sought to explain the acceleration-induced pressor effect observed.

Plasma Renin Activity: Plasma renin activity was measured in 7 normal dogs and 3 cardiac denervated dogs (Figure 15c) in each of the four cases. Results of these measurements indicated:

  (1) All 10 dogs (whether normal or cardiac denervated) had low
      values of plasma renin activity, perhaps due to their
      sedated but not anesthetized state.

  (2) Acceleration produced no consistent or significant
      changes in plasma renin activity in either the refle-
      xive or nonreflexive state.

  (3) Total autonomic blockade significantly increased (more
      than doubled) circulating levels of plasma renin activity.

Plasma Arginine Vasopressin Activity (ADH): Circulating levels of ADH were measured in 3 normal dogs and 2 cardiac denervated dogs (Figure 15d) with no significant differences in either control or test levels between these two

C-4

groups. Significance of the test responses could not be appropriately performed with the repeated-measures test chosen. Due to the difference in variances of the control and test responses, a Wilcoxon-sign test will be performed when the sample number is great enough. Results of the ADH analysis indicated:

A) Centrifugation increased ADH levels in all animals in both the reflexive and nonreflexive state.

B) The stimulus to increase the ADH level in this study was not derived from plasma osmolality changes, since there was no consistent change in osmolality with centrifugation.

C) Total autonomic blockade more than doubled resting levels of ADH, but did not appear to affect the release of ADH with centrifugation.

D) All animals had slightly elevated levels of resting ADH, perhaps due to the sedated but not anesthetized state of the animal, and

E) The signal to increase ADH levels with centrifugation was not derived solely from low volume receptors in the heart, since three of these animals had previously undergone total cardiac denervation.

Circulating Norepinephrine Levels:

The pressor response to acceleration following total autonomic blockade would tend to eliminate all autonomic neural activity, including circulating catecholamines, as the source of the increased pressure. However, the contribution of circulating catecholamines to the reflexive (unblocked) acceleration-induced pressor response remained undetermined, as did the possible influence of catecholamines on release of other pressor agents, namely renin and ADH. In addition, some recent work pointed out to us by Dr. Ziegler indicated an action of the α-blocking agent, phenoxybenzamine, used in high dosages in our study, on pre-synaptic α receptors tending to greatly increase synaptic cleft concentrations of norepinephrine, perhaps to an unblockable level. Analysis of blood samples from 4 normal dogs (Figure 15e) indicated:

C-5

1) Circulating levels of norepinephrine in these animals are at normal levels.

2) Acceleration did not produce a consistent change in plasma norepinephrine in either the reflexive or nonreflexive state.

3) Total autonomic blockade increased circulating levels of norepinephrine by an order of magnitude in each dog.

Again, significance tests will be performed when enough samples have been analyzed to perform a Wilcoxon-sign test.

Our conclusions from this set of studies, now nearing completion, are that the pressor effect we have observed with acceleration in both reflexive and nonreflexive animals, best correlates with changes seen in circulating vasopressin levels, triggered perhaps by the decrease in plasma volume seen with acceleration or by the decrease in stroke volume or upper body arterial and venous pressures with each $+2g_z$ portion of the acceleration waveform. It is also apparent from the data examined thus far that total autonomic blockade greatly increases circulating levels of plasma renin activity, circulating levels of plasma norepinephrine and vasopressin. It is thought that the pressor effects of these agents are responsible for blood pressure maintenance in the animal following total autonomic blockade. The action of the α blocker phenoxybenzamine on circulating levels of norepinephrine is a matter which we wish to explore further, but which at this time appears to not be implicated in the acceleration-induced pressor response seen in the present study.

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RESEARCH TEAM

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The formation of this research team is based on a general plan which integrates the advanced analytical techniques and instrumentation development capabilities of an interdisciplinary team, consisting of physiologists and biomedical engineers, in an effort to resolve problems associated with acceleration stress. Measurements from the invasive instrumentation of the chronically implanted animal preparation of this study are essential for identifying the

most meaningful variables for assessing acceleration-induced cardiovascular responses when less invasive measurements are eventually to be made on man. It is our belief that this basic research effort will provide the background for the design and implementation of human investigations, investigations which will lead to improve protective equipment and operational procedures for military personnel exposed to acceleration environments resulting from the optimal utilization of advanced aerospace systems.

APPENDIX B

PUBLICATIONS AND PRESENTATIONS

1. Knapp, C. F., Marquis, J. A., Evans, J. M., and Randall, D. R.: "Frequency Response of Cardiovascular Regulation in Canines to Sinusoidal Acceleration at Frequencies Below 1 Hz (Basis for Biodynamic Modeling)". Proceeding of the Models and Analogues for the Evaluation of Human Biodynamic Response, Performance and Protection Conference at Paris, France, November 6-10, 1978. Agard-CPP-253-19.

2. Randall, D. C., Evans, J., Patrick, T., and Knapp, C. F.: "Cardiovascular Responses to Coronary Occlusion in Normal vs. Cardiac Denervated Dog". The American Physiological Society, St. Louis, Missouri, June, 1978. (Abstract)

3. Knapp, C. F., Marquis, J., Evans, J., and Randall, D.: "Barostatic Regulation of the Cardiovascular System During Exposure to Low Frequency (< 0.3 Hz) Sinusoidal Acceleration". Proceedings of the Review of Air Force Sponsored Basic Research in Environmental and Acceleration Physiology, United States Air Force Academy, Colorado Springs, Colorado, September 12-13, 1978. (Abstract)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Cardiovascular regulation during whole body, sinusoidal acceleration (0.005 to 0.25 Hz) was studied. Effectiveness of barostatic regulation was compared in normal (n=9) and cardiac denervated (n=8), chronically instrumented, tranquilized (Innovar-Vet, .075 cc/kg) dogs. Amplitudes of oscillations in aortic pressure in the normal dogs were smallest, about 30 mm Hg at the lowest

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frequencies, peaked at about 50 mm Hg in the middle frequency range and tapered off to about 30 mm Hg at the highest frequencies. Pressure oscillations in the cardiac denervated animals were larger, about 70 mm Hg, across both the low and middle frequency range, tapering off sharply to 20 mm Hg at the highest frequencies. This difference was due to a greater drop in aortic pressure during the $+g_z$ portion of the cycle in the cardiac denervated vs. the normal animals. In both groups of animals, increases in peripheral resistance during $+g_z$ were of comparable magnitude and were maximal at the lowest frequencies, diminishing monotonically thereafter. The principal difference between the pressure responses of the normal and cardiac denervated dogs was that cardiac output dropped to 1.5 L/min with $+g_z$ stress in the normal vs. 1 L/min in the cardiac denervated dogs.

Experiments have also been performed to provide data for the development of suitable input/output relationships for neurally-mediated cardiovascular responses to the same acceleration stress described above. In the same normal animal in the reflexive state (n=5) and later under total autonomic blockade (nonreflexive, n=3), pressure measurements were made at five locations simultaneously: near the carotid sinus, in the jugular vein at the same level as the carotid sinus measurement, in the aortic arch and in the right and left ventricles. For both states, the double amplitude of the acceleration induced pressure disturbances at the carotid sinus was approximately 20 mm Hg/G greater than those at the aortic arch. The double amplitude of diastolic right ventricular pressure remained relatively constant across the frequency range with values of approximately 9 mm Hg/G for the reflexive state and 12 mm Hg/G for the nonreflexive state.

Lastly, a pressor response to the acceleration loadings has been observed in both reflexive and nonreflexive animals. Tentative analyses of circulating levels of various neurohumoral agents indicated that plasma renin activity and arginine vasopressin doubled with autonomic blockade, plasma norepinephrine increased by an order of magnitude and plasma volume decreased. In response to acceleration, however, only vasopressin showed a consistent increase which appeared to correlate with the increased aortic pressure.